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Trying 3106016892...Open

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LOGINID:ssspta1617mxb
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TERMINAL (ENTER 1, 2, 3, OR ?):2


* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1           Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2  Dec 17   The CA Lexicon available in the CAPLUS and CA files
 NEWS  3  Feb 06   Engineering Information Encompass files have new names
 NEWS  4  Feb 16   TOXLINE no longer being updated
 NEWS  5  Apr 23   Search Derwent WPINDEX by chemical structure
 NEWS  6  Apr 23   PRE-1967 REFERENCES NOW SEARCHABLE IN CAPLUS AND CA
 NEWS  7  May 07   DGENE Reload
 NEWS  8  Jun 20   Published patent applications (A1) are now in USPATFULL
 NEWS  9  JUL 13   New SDI alert frequency now available in Derwent's
                   DWPI and DPCI
 NEWS 10  Aug 23   In-process records and more frequent updates now in
                   MEDLINE
 NEWS 11  Aug 23   PAGE IMAGES FOR 1947-1966 RECORDS IN CAPLUS AND CA
 NEWS 12  Aug 23   Adis Newsletters (ADISNEWS) now available on STN
 NEWS 13  Sep 17   IMSworld Pharmaceutical Company Directory name change
                   to PHARMASEARCH
 NEWS 14  Oct 09   Korean abstracts now included in Derwent World Patents
                   Index
 NEWS 15  Oct 09   Number of Derwent World Patents Index updates increased
 NEWS 16  Oct 15   Calculated properties now in the REGISTRY/ZREGISTRY File
 NEWS 17  Oct 22   Over 1 million reactions added to CASREACT
 NEWS 18  Oct 22   DGENE GETSIM has been improved
 NEWS 19  Oct 29   AAASD no longer available

 NEWS EXPRESS  August 15 CURRENT WINDOWS VERSION IS V6.0c,
               CURRENT MACINTOSH VERSION IS V6.0 (ENG) AND V6.0J (JP),
               AND CURRENT DISCOVER FILE IS DATED 07 AUGUST 2001
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FILE 'HOME' ENTERED AT 18:18:41 ON 15 NOV 2001

=> file caba
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COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.15       0.15

FILE 'CABA' ENTERED AT 18:18:52 ON 15 NOV 2001
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FILE COVERS 1973 TO 1 Nov 2001 (20011101/ED)

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> s 991412046/rn
'RN' IS NOT A VALID FIELD CODE
L1             0 991412046/RN

=> s 991412046/an
L2             0 991412046/AN

=> s Mak/au
L3             0 MAK/AU

=> s clinical experience and ketogenic diet
         87824 CLINICAL
             2 CLINICALS
         87825 CLINICAL
                 (CLINICAL OR CLINICALS)
         31330 EXPERIENCE
         12213 EXPERIENCES
         41858 EXPERIENCE
                 (EXPERIENCE OR EXPERIENCES)
           457 CLINICAL EXPERIENCE
                 (CLINICAL(W)EXPERIENCE)
           218 KETOGENIC
        132210 DIET
         84944 DIETS
        164316 DIET
                 (DIET OR DIETS)
            80 KETOGENIC DIET
                 (KETOGENIC(W)DIET)
L4             1 CLINICAL EXPERIENCE AND KETOGENIC DIET

=> d l4

L4   ANSWER 1 OF 1  CABA COPYRIGHT 2001 CABI
AN   1999:136034  CABA
DN   991412046
TI   Clinical experience of ketogenic
     diet on children with refractory epilepsy
AU   Mak SukChun; Chi ChingShiang; Wan ChuJen; Mak, S. C.; Chi, C. S.; Wan, C.
     J.
CS   Department of Pediatrics, Taichung Veterans General Hospital, 160, Chung
     Kang Road, Sec. 3, Taichung, Taiwan.
SO   Acta Paediatrica Sinica, (1999) Vol. 40, No. 2, pp. 97-100. 11 ref.
     ISSN: 0001-6578
DT   Journal
LA   English


=> d ab
```

L4 ANSWER 1 OF 1 CABA COPYRIGHT 2001 CABI

AB 13 children with refractory epilepsy received a **ketogenic diet** (medium chain triglyceride oil diet) as an alternative therapy since September 1997. Their seizure patterns included (1) generalized tonic-clonic seizures, (2) myoclonic seizures, (3) generalized tonic plus atonic seizures, (4) complex partial seizures, (5) generalized clonic plus atonic plus myoclonic seizures, (6) head nodding plus myoclonic plus gelastic seizures, and (7) generalized tonic-clonic plus myoclonic plus atonic seizures. Clinical observation 1 month after the diet revealed that 53.8% of the patients had a >75% reduction in seizure frequency and 76.9% of the patients had a >50% reduction in seizure frequency. Six patients had some degrees of improvement in cognitive function and/or school performances. The most common side effects were body weight loss (n=6) and diarrhoea (n=5). Others included bad temper (n=1), abdominal cramps (n=2), nausea (n=2), bad body smell (n=1), and renal stones (n=1). Even after discontinuation of the diet, 61.5% of patients still had a >50% reduction in seizure frequency. It is concluded that the **ketogenic diet** deserves a trial in children with refractory epilepsy.

=> file medline

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	3.08	3.23

FILE 'MEDLINE' ENTERED AT 18:21:07 ON 15 NOV 2001

FILE LAST UPDATED: 15 NOV 2001 (20011115/UP). FILE COVERS 1958 TO DATE.

On April 22, 2001, MEDLINE was reloaded. See HELP RLOAD for details.

MEDLINE now contains IN-PROCESS records. See HELP CONTENT for details.

MEDLINE is now updated 4 times per week. A new current-awareness alert frequency (EVERYUPDATE) is available. See HELP UPDATE for more information.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2001 vocabulary. Enter HELP THESAURUS for details.

The OLDMEDLINE file segment now contains data from 1958 through 1965. Enter HELP CONTENT for details.

Left, right, and simultaneous left and right truncation are available in the Basic Index. See HELP SFIELDS for details.

THIS FILE CONTAINS CAS REGISTRY NUMBERS FOR EASY AND ACCURATE SUBSTANCE IDENTIFICATION.

=> s 96063810/an
L5 1 96063810/AN

=> d

L5 ANSWER 1 OF 1 MEDLINE
AN **96063810** MEDLINE
DN 96063810 PubMed ID: 8534410
TI Acetyl-L-carnitine in Alzheimer disease: a short-term study on CSF

neurotransmitters and neuropeptides.
AU Bruno G; Scaccianoce S; Bonamini M; Patacchioli F R; Cesarino F; Grassini P; Sorrentino E; Angelucci L; Lenzi G L
CS Dipartimento di Scienze Neurologiche, Universita di Roma La Sapienza, Italy.
SO ALZHEIMER DISEASE AND ASSOCIATED DISORDERS, (1995 Fall) 9 (3) 128-31. Journal code: ALZ; 8704771. ISSN: 0893-0341.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199602
ED Entered STN: 19960221
Last Updated on STN: 19980206
Entered Medline: 19960207

=> d ab

L5 ANSWER 1 OF 1 MEDLINE
AB Acetyl-L-carnitine (ALCAR) is a drug currently under investigation for Alzheimer disease (AD) therapy. ALCAR seems to exert a number of central nervous system (CNS)-related effects, even though a clear pharmacological action that could explain clinical results in AD has not been identified yet. The aim of this study was to determine cerebrospinal fluid (CSF) and plasma biological correlates of ALCAR effects in AD after a short-term, high-dose, intravenous, open treatment. Results show that ALCAR CSF levels achieved under treatment were significantly higher than the ones at baseline, reflecting a good penetration through the blood-brain barrier and thus a direct CNS challenge. ALCAR treatment produced no apparent change on CSF classic neurotransmitters and their metabolite levels (homovanillic acid, 5-hydroxyindoleacetic acid, MHPG, dopamine, choline). Among CSF peptides, while corticotropin-releasing hormone and adrenocorticotropic hormone remained unchanged, beta-endorphins significantly decreased after treatment; plasma cortisol levels matched this reduction. Since both CSF beta-endorphins and plasma cortisol decreased, one possible explanation is that ALCAR reduced the AD-dependent hypothalamic-pituitary-adrenocortical (HPA) axis hyperactivity. At present, no clear explanation can be proposed for the specific mechanism of this action.

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Welcome to STN International! Enter x:x
LOGINID:ssspta1617mxb
PASSWORD:
* * * * * * RECONNECTED TO STN INTERNATIONAL * * * * * *
SESSION RESUMED IN FILE 'MEDLINE' AT 18:26:48 ON 15 NOV 2001
FILE 'MEDLINE' ENTERED AT 18:26:48 ON 15 NOV 2001

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	1.10	4.33

=> file embase biosis medline caplus uspatfull

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	1.70	4.93

FILE 'EMBASE' ENTERED AT 18:28:01 ON 15 NOV 2001

FILE 'BIOSIS' ENTERED AT 18:28:01 ON 15 NOV 2001

FILE 'MEDLINE' ENTERED AT 18:28:01 ON 15 NOV 2001

FILE 'CAPLUS' ENTERED AT 18:28:01 ON 15 NOV 2001

FILE 'USPATFULL' ENTERED AT 18:28:01 ON 15 NOV 2001

=> s ketogenic diet and alzheimer
L6 4 KETOGENIC DIET AND ALZHEIMER

=> dup rem l6
PROCESSING COMPLETED FOR L6
L7 4 DUP REM L6 (0 DUPLICATES REMOVED)

=> d l7 1-4 ab bib kwic

L7 ANSWER 1 OF 4 USPATFULL
AB Compositions comprising ketone bodies and/or their metabolic precursors are provided that are suitable for administration to humans and animals and which have the properties of, inter alia, (i) increasing cardiac efficiency, particularly efficiency in use of glucose, (ii) for providing energy source, particularly in diabetes and insulin resistant states and (iii) treating disorders caused by damage to brain cells, particularly by retarding or preventing brain damage in memory associated brain areas such as found in **Alzheimer**'s and similar conditions.

These compositions may be taken as nutritional aids, for example for athletes, or for the treatment of medical conditions, particularly those associated with poor cardiac efficiency, insulin resistance and neuronal damage. The invention further provides methods of treatment and novel esters and polymers for inclusion in the compositions of the invention.

AN 2001:205943 USPATFULL
TI Therapeutic compositions
IN Veech, Richard L., Rockville, MD, United States
PA BTG International Limited (U.S. corporation)
PI US 2001041736 A1 20011115
AI US 2001-843694 A1 20010430 (9)
RLI Continuation of Ser. No. US 1999-397100, filed on 16 Sep 1999, PENDING
Continuation of Ser. No. WO 1998-US5072, filed on 17 Mar 1998, UNKNOWN
PRAI US 1997-40858 19970317 (60)
DT Utility
FS APPLICATION
LREP Nixon & Vanderhye P.C., 8th Floor, 1100 N. Glebe Rd., Arlington, VA, 22201
CLMN Number of Claims: 31
ECL Exemplary Claim: 1
DRWN 2 Drawing Page(s)
LN.CNT 1889
AB . . . damage to brain cells, particularly by retarding or preventing brain damage in memory associated brain areas such as found in **Alzheimer**'s and similar conditions.
SUMM . . . damage to brain cells, particularly by retarding or preventing brain damage in memory associated brain areas such as found in **Alzheimer**'s and similar conditions. These compositions may be taken as nutritional aids, for example for athletes, or for the treatment of. . .
SUMM [0011] **Alzheimer**'s disease is a genetically heterogeneous group of progressively fatal neurological diseases characterized pathologically by accumulation of amyloid plaques in brain and clinically by impairment of recent memory leading to dementia and death.
In addition to the cases of **Alzheimer**'s disease linked to genetic causes, sporadic cases, without an apparent family history of the disease, also occur. For example pathological changes characteristic
of **Alzheimer**'s disease occur after head trauma (73) or after inflammatory diseases stimulating production of the cytokine interleukin-1 (97).
SUMM [0013] The diagnosis of **Alzheimer**'s disease is made clinically by this impairment in recent memory, associated with lesions in the hippocampal portion of the temporal. . .
SUMM . . . is not necessarily a clear, bright line between the pathological brain changes and the memory deficits which occur prematurely in **Alzheimer**'s disease and the pathological changes in brain anatomy and memory function which are found in the "normal" aging population. Rather. . . decreased glucose tolerance signifying an inability to metabolize glucose. In such situations, treatments aimed at rectifying the pathophysiological processes of **Alzheimer**'s disease, would be expected to be applicable to the correction of the metabolic effects associated with normal aging.
SUMM [0015] While **Alzheimer**'s disease of the familial or the sporadic type is the major dementia found in the aging population, other
types of. . . of Lewy body type, dementia of Parkinsonism with frontal atrophy, progressive supranuclear palsy and corticobasal degeneration and Downs syndrome associated **Alzheimers'**. Plaque formation is also seen in the spongiform encephalopathies such as CJD, scrapie and BSE. The present invention is directed. . .
SUMM [0016] Many of these aforesaid apparently unrelated conditions have the hyperphosphorylated tau proteins found in **Alzheimer**'s disease (69), opening up the possibility that the same kinase which

phosphorylated tau would also phosphorylate the PDH complex producing a similar deficiency in mitochondrial energy production and acetyl choline synthesis found in **Alzheimer**'s disease but involving other brain regions. The present inventor has determined that in this respect treatments applicable to **Alzheimer**'s disease might be applied to these diseases as well. In addition, the inventor has determined that such treatment will also. . .

SUMM [0017] At present there is no effective treatment for **Alzheimer** s disease. Research efforts are focused on defining its genetic cause but to date there has been no succesful gene therapy. Genetic studies have linked **Alzheimer**'s disease with Mongolism and in its early onset form to locus on chromosome 21 causing accumulation of amyloid precursor protein. . . transmembrane glycoprotein existing in 8 isoforms. Numerous fragments of this protein are derived by proteolysis and the plaques characteristic of **Alzheimer**'s disease have been shown to contain accumulation of the oligomer of .beta. amyloid protein (A.beta..sub.1-42). An early onset autosomally dominant form of **Alzheimer**'s disease has also been related to a presenilin 1 locus on chromosome 14.

SUMM [0018] A late onset form of **Alzheimer**'s disease is associated with the type 4 allele of apolipoprotein E (69,98) on chromosome 19, although other workers suggest that. . . amounts of amyloid precursor protein over 18 months of age showed hippocampal degeneration with many of the pathological characteristics of **Alzheimer**'s disease (90).

SUMM [0019] The current status of knowledge on the defective genes and gene products in **Alzheimer**'s disease has recently been summarized (Table 1 of ref. 96).

Chromosome	Gene Defect	Age of Onset	A.beta. Phenotype
21	.beta.APP. . .		

SUMM [0020] It is clear from the above table that the common phenotype associated with the genetic forms of **Alzheimer**'s disease is the accumulation of the amyloid peptide A.beta..sub.1-42 (96). It is this A.beta..sub.1-42 which inactivates PDH thus impairing mitochondrial. . . tangles comprised of hyperphosphorylated tau protein, and decreased brain acetyl choline levels, cell death is the fourth pathological characteristic of **Alzheimer**'s disease. These pathological characteristics can be related, at least in part, to excess A.beta..sub.1-42 and its inhibition of PDH.

SUMM . . . to hippocampus in the anterior portion of the limbic system of brain. However the progress in the molecular biology of **Alzheimer**'s disease has caused the search for new therapies to concentrate upon four major areas (96): (i) protease inhibitors that partially. . .

SUMM . . . when translocated into cytoplasm, a source of cytoplasmic acetyl CoA required to remedy the deficiency of acetyl choline characteristic of **Alzheimer**'s brains.

SUMM [0024] There has been long experience with **ketogenic diets** in children treated for epilepsy. Such diets are however unsuitable for use in adults due to adverse efects on the. . .

SUMM . . . IIoshi and collaborators (77, 78) strongly suggests that a part

of the amyloid protein whose accumulation is the hallmark of **Alzheimer**'s disease, A.beta..sub.1-42, acts as a mitochondrial histidine protein kinase which phosphorylates and inactivates the pyruvate dehydrogenase multienzyme complex. The PDH. . .

SUMM . . . a number of forms of injury, and the death of these cells is the hallmark both clinically and pathologically of **Alzheimer**'s disease.

SUMM [0034] It is the inventors hypothesis that in **Alzheimer**'s disease, where there is a block at PDH which prevents the normal energy production from glucose, if one can provide. . .

SUMM [0045] The **ketogenic diet**, comprised mainly of lipid, has been used since 1921 for the treatment of epilepsy in children, particularly myoclonic and akinetic. . .

SUMM [0046] An example of a traditional 1500/day calorie **ketogenic diet** recommended by the Marriott Corp. Health Care Services, Pediatric Diet Manual, Revised August 1987 as suitable for a 4-6 year. . .

SUMM . . . achieved are not be subject to variation caused by noncompliant ingestion of carbohydrate, as is the case with the present **ketogenic diet**. Rather, they would simply be an additive to the normal diet, given in sufficient amounts to produce a sustained blood. . . case of resistant childhood epilepsy, blood levels of 2 mM are currently thought to be sufficient. In the case of **Alzheimer**'s disease, attempts could be made to keep levels at 7.5 mM achieved in the fasting man studies, in an effort to provide alternative energy and acetyl CoA supplies to brain tissue in **Alzheimer**'s patients where PDH capacity is impaired because of excess amounts of A.beta..sub.1-42 amyloid peptide (77, 78).

SUMM . . . range of use in a greater variety of patients, including: type II diabetes to prevent hypoglycemic seizures and coma, in **Alzheimer**'s disease and other neurodegenerative states to prevent death of nerve cells eg. hippocampal cells, and in refractory epilepsy due to. . .

SUMM . . . heart and brain tissue, but not liver. Hence the fatty liver, which may be an untoward side effect of the **ketogenic diet**, is avoided. Thirdly, the ability to include carbohydrate in the dietary formulations increases the chance of compliance and opens up practical therapeutic approaches to type II diabetics where insulin is high, making the known **ketogenic diet** unworkable.

SUMM . . . to 7.5 mM level and above, particularly when attempting to arrest the death of brain cells in diseases such as **Alzheimer**'s. While dead cells cannot be restored, arrest of further deterioration and at least some restoration of function is to be. . .

SUMM . . . retarding or preventing nerve cell damage or death related disorders, particularly neurodegenerative disorders such as memory associated disorders such as **Alzheimer**'s, seizure and related states such as encepalophies such as CJD and BSE.

SUMM [0091] Where the therapy is aimed at seizure related disorders, such as refractory epilepsy as is treated by the **ketogenic diet**, therapy is improved by use of ketone bodies, their polymers or esters or precursors such as butandiol compounds, due to. .

SUMM . . . such as those related to neurotoxic conditions such as presence of amyloid protein, eg. a memory associated disorder such as **Alzheimer**'s disease, or epileptic seizures, comprising

administering to that person least one at least one of a materials for use in. . .

SUMM [0113] The amount of ketone bodies used in treatment of neurodegeneration such as **Alzheimer**'s and Parkinsonism will preferably elevate blood levels to 0.5 mM to 20 mM, eg 2 mM to 7.5 mM as. . .

SUMM [0114] It will be realised that treatment for neurodegenerative diseases such as **Alzheimer**'s will most effectively be given soon after identifying patient's with a predisposition to develop the disease. Thus treatment for **Alzheimers**' most effectively follows a positive test result for one or more conditions selected from the group (i) mutations in the. . . the presenilin gene on chromosome 14, (iii) presence of isoforms of apolipoprotein E. Other tests shown to be indicative of **Alzheimer**'s will of course be applicable.

SUMM . . . twelvth aspects of the invention comprising one of (i) total fasting of the individual and (ii) feeding the individual a **ketogenic diet** eg. of 60-80% lipid with carbohydrate content 20% or less by weight.

SUMM [0118] In all these treatments other than the **ketogenic diet** there is the improvement that a method of avoiding drop in blood ketones which accompanies the ingestion of excess carbohydrate.

.

.

DETD [0130]

TABLE 2

Sample 1500 calorie **ketogenic diet** using ketone bodies, their esters or polymers. The ketones were assumed to contain 6 kcal/g, fats 9 kcal/g, carbohydrate and protein 4. . .

DETD [0202] 56. Amari, A., N. C. Grace, W. W. Fisher. Achieving and maintaining compliance with the **ketogenic diet**. J Appl Behav Anal 28: 341-342, 1995.

DETD [0207] 61. Brion, J. P. The neurobiology of **Alzheimer**'s disease. Acta Clin Belg 51: 80-90 1996.

DETD . . . C., F. Crawford, H. Houlden, A. Warren, D. Hughes, L. Fidani, A. Goate, M. Rossor, P. Roques, J. Hardy Early-onset **Alzheimer**'s disease caused by mutations at codon 717 of the beta-amyloid precursor protein gene. Nature 353: 844-846, 1991.

DETD . . . D. Roses, J. L. Haines, M. A. Pericak-Vance. Gene dose of apolipoprotein E type 4 allele and the risk of **Alzheimer**'s disease in late onset families (see comments), Science 261: 921-923, 1993.

DETD . . . K. Warrington, P. A. Freeborough, P. Hartikainen, A. M. Kennedy, J. M. Stevens, M. N. Rossor. Presymptomatic hippocampal atrophy in **Alzheimer**'s disease. A longitudinal MRI study. Brain 119: 2001-2007, 1996

DETD . . . Giuffra, A. Haynes, N. Irving, L. James. Segregation of a missense mutation in the amyloid precursor protein gene with familial **Alzheimer**'s disease (see comments). Nature 349: 704-706, 1991.

DETD . . . McKenzie, G. W. Roberts, W. S. Griffin. Altered beta-APP metabolism after head injury and its relationship to the aetiology of **Alzheimer**'s disease. Acta Neurochir Suppl (Wien). 66:96-102,1996.

DETD . . . D. Adams, R. T. Cline, C. A. Phillips, A. Goate. Complete analysis of the presenilin 1 gene in early onset **Alzheimer**'s

disease. Neuroreport. 7: 801-805, 1996.
DETD [0231] Effect of low-carbohydrate-**ketogenic diet** on metabolic and hormonal responses to graded exercise in men. J Physiol Pharmacol 47: 361-371, 1996.
DETD [0236] 88. Nebeling, L. C., E. Lerner. Implementing a **ketogenic diet** based on medium-chain triglyceride oil in pediatric patents with cancer. J Am Diet Assoc 95: 693-697, 1995.
DETD , [0237] 89. Nebeling, L. C., F. Miraldi, S. B. Shurin, E. Lerner. Effects of a **ketogenic diet** on tumor metabolism and nutritional status in pediatric oncology patents: two case reports. J Am Coll Nutr 14: 202-208, 1995.
DETD [0240] 92. Paradis, E., H. Douillard, M. Koutroumanis, C. Goodyer, A. LeBlanc. Amyloid beta peptide of **Alzheimer**'s disease downregulates Bcl-2 and upregulates bax expression in human neurons. J Neurosci 16:7533-7539, 1996.
DETD [0242] 94. Rossor, M. N. Catastrophe, chaos and **Alzheimer**'s disease. The FE Williams Lecture. J R Coll Physicians Lond 29: 412-418, 1995.
DETD [0244] 96. Selkoe, D. J. **Alzheimer**'s disease: genotypes, phenotypes, and treatments. Science 275: 630-631, 1997.
DETD . . . Griffin. In vivo and in vitro evidence supporting a role for the inflammatory cytokine interleukin-1 as a driving force in **Alzheimer** pathogenesis. Neurobiol Aging 17: 761-766, 1996.
DETD [0246] 98. Strittmatter, W. J., A. D. Roses. Apolipoprotein E and **Alzheimer** disease. Proc Natl Acad Sci U.S.A. 92: 4725-4727, 1995.
DETD . . . Lendon, G. Prihar, J. C. Morris, J. Hardy, A. Goate. Polymorphism in AACT gene may lower age of onset of **Alzheimer**'s disease. Neuroreport. 7: 534-536, 1996.
DETD [0256] 108. Wang, J. Z., I. Grundke-Iqbal, K. Iqbal. Restoration of biological activity of **alzheimer** abnormally phosphorylated tau by dephosphoryulation with protein phosphatase-2A, -2B and -1. Brain Res Mol Brain Res 38: 200-208, 1996.

L7 ANSWER 2 OF 4 USPATFULL
AB Compositions comprising ketone bodies and/or their metabolic precursors are provided that are suitable for administration to humans and animals and which have the properties of, inter alia, (i) increasing cardiac efficiency, particularly efficiency in use of glucose, (ii) for providing energy source, particularly in diabetes and insulin resistant states and (iii) treating disorders caused by damage to brain cells, particularly by retarding or preventing brain damage in memory associated brain areas such as found in **Alzheimer**'s and similar conditions.

These compositions may be taken as nutritional aids, for example for athletes, or for the treatment of medical conditions, particularly those associated with poor cardiac efficiency, insulin resistance and neuronal damage. The invention further provides methods of treatment and novel esters and polymers for inclusion in the compositions of the invention.
AN 2001:134247 USPATFULL
TI Therapeutic compositions (II)
IN Veech, Richard Lewis, Rockville, MD, United States
PI US 2001014696 A1 20010816
AI US 2001-799124 A1 20010306 (9)

RLI Continuation of Ser. No. WO 1999-US21015, filed on 15 Sep 1999, UNKNOWN
PRAI US 1998-100371 19980915 (60)
DT Utility
FS APPLICATION
LREP Nixon & Vanderhye, Eighth Floor, 1100 North Glebe Road, Arlington, VA, 22201-4714
CLMN Number of Claims: 18
ECL Exemplary Claim: 1
DRWN 1 Drawing Page(s)
LN.CNT 1376
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB . . . damage to brain cells, particularly by retarding or preventing brain damage in memory associated brain areas such as found in **Alzheimer**'s and similar conditions.

SUMM . . . caused by damage to neuronal cells, e.g. CNS cells, particularly by retarding or preventing brain damage such as found in **Alzheimer**'s and Parkinsonism and similar diseases and conditions.

SUMM . . . number of disease processes involve damage by free radicals among which are the neurological diseases: Parkinson's disease, amyotrophic lateral sclerosis, **Alzheimer**'s disease and cerebral ischemia. In addition excessive free radical damage has been implicated as playing a role in coronary reperfusion,. . .

SUMM . . . The present invention's improved efficacy in raising levels, particularly blood levels, of ketone bodies provides therapeutic effects of the classical **ketogenic diet**, which is not itself found to be toxic in children, with none of the side effects that render that unused. . .

SUMM [0031] Where the therapy is aimed at seizure related disorders, such as refractory epilepsy as is treated by the **ketogenic diet**, therapy is improved by use of cyclic oligomers, due to the reduction or elimination of both high lipid and carbohydrate. . .

SUMM . . . those related to neurotoxic conditions such as presence of amyloid protein, e.g. a memory or movement associated disorder such as **Alzheimer**'s or Parkinson's diseases, or epileptic seizures, comprising administering to that person at least one of the materials for use in. . .

SUMM . . . Hoshi and collaborators (77, 78) strongly suggests that a part of the amyloid protein whose accumulation is the hallmark of **Alzheimer**'s disease, A.beta..sub.1-42, acts to stimulate mitochondrial histidine protein kinase which phosphorylates and inactivates the pyruvate dehydrogenase multienzyme complex. The PDH. . .

SUMM [0038] In the copending application WO 98/41201, `Therapeutic compositions`, it is the inventor's hypothesis that in **Alzheimer**'s disease, where there is a block at PDH which prevents the normal energy production from glucose, if one can provide. . .

SUMM [0045] The **ketogenic diet**, comprised mainly of lipid, has been used since 1921 for the treatment of epilepsy in children, particularly myoclonic and akinetic. . .

SUMM . . . ketones achieved are not subject to variation caused by noncompliant ingestion of carbohydrate, as is the case with the present **ketogenic diet**. Rather, they would simply be an additive to the normal diet, given in sufficient amounts to produce a sustained blood. . . case of resistant childhood epilepsy, blood levels of 2 mM are currently thought to be sufficient. In the case of **Alzheimer**'s disease, attempts could even be made to keep levels at 7.5 mM or more, as achieved in the fasting man studies, in an effort

to provide alternative energy and acetyl CoA supplies to brain tissue in **Alzheimer**'s patients where PDH capacity is impaired because of excess amounts of A.beta..sub.1-42 amyloid peptide (77, 78).

SUMM . . . a greater variety of patients, including but not limited to: type II diabetes to prevent hypoglycemic seizures and coma, in **Alzheimer**'s disease and other neurodegenerative states to prevent death of nerve cells e.g. hippocampal cells, and in refractory epilepsy due to. . .

SUMM . . . heart and brain tissue, but not liver. Hence the fatty liver, which may be an untoward side effect of the **ketogenic diet**, is avoided. Thirdly, the ability to include carbohydrate in the dietary formulations increases the chance of compliance and opens up practical therapeutic approaches to type II diabetics where insulin is high, making the known **ketogenic diet** unworkable.

SUMM . . . to 7.5 mM level and above, particularly when attempting to arrest the death of brain cells in diseases such as **Alzheimer**'s and Parkinsonism. While dead cells cannot be restored, arrest of further deterioration and at least some restoration of function is. . .

SUMM [0070] The total amount of ketone bodies used in treatment of neurodegeneration such as **Alzheimer**'s and Parkinsonism will preferably elevate blood levels of ketone bodies by from 0.5 mM to 20 mM. The present inventor. . .

SUMM [0071] It will be realised that treatment for neurodegenerative diseases such as **Alzheimer**'s or Parkinsonism will most effectively be given soon after identifying patient's with a predisposition to develop the disease. Thus treatment for **Alzheimers**' most effectively follows a positive test result for one or more conditions selected from the group (i) mutations in the. . . the presenilin gene on chromosome 14, (iii) presence of isoforms of apolipoprotein E. Other tests shown to be indicative of **Alzheimer**'s will of course be applicable.

DETD [0090]

TABLE 2

Sample 1500 calorie **ketogenic diet** using cyclic oligomer (I) of invention. The cyclic oligomer is assumed to contain 6 kcal/g fats, 9 kcal/g carbohydrate and 4 kcal/g. . .

DETD [0153] 56. Amari, A., N. C. Grace, W. W. Fisher. Achieving and maintaining compliance with the **ketogenic diet**. J Appl Behav Anal 28: 341-342, 1995.

DETD [0158] 61. Brion, J. P. The neurobiology of **Alzheimers** disease. Acta Clin Belg 51: 80-90 1996.

DETD . . . C., F. Crawford, H. Houlden, A. Warren, D. Hughes, L. Fidani, A. Goate, M. Rossor, P. Roques, J. Hardy Early-onset **Alzheimer**'s disease caused by mutations at codon 717 of the beta-amyloid precursor protein gene. Nature 353: 844-846, 1991.

DETD . . . D. Roses, J. L. Haines, M. A. Pericak-Vance. Gene dose of apolipoprotein E type 4 allele and the risk of **Alzheimer**'s disease in late onset families (see comments), Science 261: 921-923, 1993.

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in **Alzheimer**'s disease. A longitudinal MRI study. Brain 119: 2001-2007, 1996

DETD . . . Giuffia, A. Haynes, N. Irving, L. James. Segregation of a missense mutation in the amyloid precursor protein gene with familial **Alzheimer**'s disease (see comments). Nature 349: 704-706, 1991.

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DETD [0185] 88. Nebeling, L. C., E. Lerner. Implementing a **ketogenic diet** based on medium-chain triglyceride oil in pediatric patents with cancer. J Am Diet Assoc 95: 693-697, 1995.

DETD [0186] 89. Nebeling, L. C., F. Miraldi, S. B. Shurin, E. Lerner. Effects of a **ketogenic diet** on tumor metabolism and nutritional status in pediatric oncology patents: two case reports. J Am Coll Nutr 14: 202-208, 1995.

DETD [0189] 92. Paradis, E., H. Douillard, M. Koutroumanis, C. Goodyer, A. LeBlanc. Amyloid beta peptide of **Alzheimer**'s disease downregulates Bcl-2 and upregulates bax expression in human neurons. J Neurosci 16:7533-7539, 1996.

DETD [0191] 94. Rossor, M. N. Catastrophe, chaos and **Alzheimer**'s disease. The FE Williams Lecture. J R Coll Physicians Lond 29: 412-418, 1995.

DETD [0193] 96. Selkoe, D. J. **Alzheimer**'s disease: genotypes, phenotypes, and treatments. Science 275: 630-631, 1997.

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DETD . . . Lendon, G. Prihar, J. C. Morris, J. Hardy, A. Goate. Polymorphism in AACT gene may lower age of onset of **Alzheimer**'s disease. Neuroreport. 7: 534-536, 1996.

DETD [0205] 108. Wang, J. Z., I. Grundke-Iqbal, K. Iqbal. Restoration of biological activity of **alzheimer** abnormally phosphorylated tau by dephosphoryulation with protein phosphatase-2A, -2B and -1. Brain Res Mol Brain Res 38: 200-208, 1996.

CLM What is claimed is:

. . . in claim 7 or 8 wherein the method is performed on a patient needing therapy for one or more of **Alzheimer**'s, Parkinsonism, Amylotrophic lateral sclerosis, Epilepsy, Free radical disease, Heart failure, Type II diabetes, deficiency or blockage of pyruvate dehydrogenase, inability. . .

L7 ANSWER 3 OF 4 USPATFULL

AB Compositions comprising ketone bodies and/or their metabolic precursors are provided that are suitable for administration to humans and animals and which have the properties of, inter alia, (i) increasing cardiac efficiency, particularly efficiency in use of glucose, (ii) for

providing energy source, particularly in diabetes and insulin resistant states and (iii) treating disorders caused by damage to brain cells, particularly by retarding or preventing brain damage in memory associated brain areas such as found in **Alzheimer**'s and similar conditions.

These compositions may be taken as nutritional aids, for example for athletes, or for the treatment of medical conditions, particularly those associated with poor cardiac efficiency, insulin resistance and neuronal damage. The invention further provides methods of treatment and novel esters and polymers for inclusion in the compositions of the invention.

AN 2001:202234 USPATFULL
TI Therapeutic compositions
IN Veech, Richard Lewis, Rockville, MD, United States
PA BTG International Limited, London, United Kingdom (non-U.S. corporation)
PI US 6316038 B1 20011113
AI US 1999-397109 19990916 (9)
RLI Continuation of Ser. No. WO 1998-GB5072, filed on 17 Mar 1998
PRAI US 1997-40858 19970317 (60)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Reamer, James H.
LREP Nixon & Vanderhye
CLMN Number of Claims: 2
ECL Exemplary Claim: 1
DRWN 1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 1821
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SUMM . . . damage to brain cells, particularly by retarding or preventing brain damage in memory associated brain areas such as found in **Alzheimer**'s and similar conditions. These compositions may be taken as nutritional aids, for example for athletes, or for the treatment of. . .
SUMM **Alzheimer**'s disease is a genetically heterogeneous group of progressively fatal neurological diseases characterized pathologically by accumulation of amyloid plaques in brain and clinically by impairment of recent memory leading to dementia and death. In addition to the cases of **Alzheimer**'s disease linked to genetic causes, sporadic cases, without an apparent family history of the disease, also occur. For example pathological changes characteristic of **Alzheimer**'s disease occur after head trauma (73) or after inflammatory diseases stimulating production of the cytokine interleukin-1 (97).
SUMM The diagnosis of **Alzheimer**'s disease is made clinically by this impairment in recent memory, associated with lesions in the hippocampal portion of the temporal. . .
SUMM . . . is not necessarily a clear, bright line between the pathological brain changes and the memory deficits which occur prematurely in **Alzheimer**'s disease and the pathological changes in brain anatomy and memory function which are found in the "normal" aging population. Rather. . . decreased glucose tolerance signifying an inability to metabolize glucose. In such situations, treatments aimed at rectifying the pathophysiological processes of **Alzheimer**'s disease, would be expected to be applicable to the

correction of the metabolic effects associated with normal aging.

SUMM While **Alzheimer**'s disease of the familial or the sporadic type is the major dementia found in the aging population, other types of. . . of Lewy body type, dementia of Parkinsonism with frontal atrophy, progressive supranuclear palsy and corticobasal degeneration and Downs syndrome associated **Alzheimers'**. Plaque formation is also seen in the spongiform encephalopathies such as CJD, scrapie and BSE. The present invention is directed. . .

SUMM Many of these aforesaid apparently unrelated conditions have the hyperphosphorylated tau proteins found in **Alzheimer**'s disease (69), opening up the possibility that the same kinase which phosphorylated tau would also phosphorylate the PDH complex producing a similar deficiency in mitochondrial energy production and acetyl choline synthesis found in **Alzheimer**'s disease but involving other brain regions. The present inventor has determined that in this respect treatments applicable to **Alzheimer**'s disease might be applied to these diseases as well. In addition, the inventor has determined that such treatment will also. . .

SUMM At present there is no effective treatment for **Alzheimer**'s disease. Research efforts are focused on defining its genetic cause but to date there has been no succesful gene therapy. Genetic studies have linked **Alzheimer**'s disease with Mongolism and in its early onset form to locus on chromosome 21 causing accumulation of amyloid precursor protein. . . transmembrane glycoprotein existing in 8 isoforms. Numerous fragments of this protein are derived by proteolysis and the plaques characteristic of **Alzheimer**'s disease have been shown to contain accumulation of the oligomer of .beta. amyloid protein (A.beta..sub.1-42). An early onset autosomally dominant form of **Alzheimer**'s disease has also been related to a presenilin 1 locus on chromosome 14.

SUMM A late onset form of **Alzheimer**'s disease is associated with the type 4 allele of apolipoprotein E (69,98) on chromosome 19, although other workers suggest that. . . amounts of amyloid precursor protein over 18 months of age showed hippocampal degeneration with many of the pathological characteristics of **Alzheimer**'s disease (90).

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SUMM It is clear from the above table that the common phenotype associated with the genetic forms of **Alzheimer**'s disease is the accumulation of the amyloid peptide A.beta..sub.1-42 (96). It is this A.beta..sub.1-42 which inactivates PDH thus impairing mitochondrial. . . tangles comprised of hyperphosphorylated tau protein, and decreased brain acetyl choline levels, cell death is the fourth pathological characteristic of **Alzheimer**'s disease. These pathological characteristics can be related, at least in part, to excess A.beta..sub.1-42 and its inhibition of PDH.

SUMM . . . to hippocampus in the anterior portion of the limbic system of brain. However the progress in the molecular biology of **Alzheimer**'s disease has caused the search for new therapies to concentrate upon four major areas (96): (i) protease inhibitors that partially. . .

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SUMM . . . achieved are not be subject to variation caused by noncompliant ingestion of carbohydrate, as is the case with the present **ketogenic diet**. Rather, they would simply be an additive to the normal diet, given in sufficient amounts to produce a sustained blood. . . case of resistant childhood epilepsy, blood levels of 2 mM are currently thought to be sufficient. In the case of **Alzheimer**'s disease, attempts could be made to keep levels at 7.5 mM achieved in the fasting man studies, in an effort to provide alternative energy and acetyl CoA supplies to brain tissue in **Alzheimer**'s patients where PDH capacity is impaired because of excess amounts of A.beta..sub.1-42 amyloid peptide (77, 78).

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SUMM . . . retarding or preventing nerve cell damage or death related disorders, particularly neurodegenerative disorders such as memory associated disorders such as **Alzheimer**'s, seizure and related states such as encepalophies such as CJD and BSE.

SUMM Where the therapy is aimed at seizure related disorders, such as refractory epilepsy as is treated by the **ketogenic diet**, therapy is improved by use of ketone bodies, their polymers or esters or precursors such as butandiol compounds, due to. .

SUMM . . . such as those related to neurotoxic conditions such as presence

of amyloid protein, eg. a memory associated disorder such as **Alzheimer**'s disease, or epileptic seizures, comprising administering to that person least one at least one of a materials for use in. . .

SUMM The amount of ketone bodies used in treatment of neurodegeneration such as **Alzheimer**'s and Parkinsonism will preferably elevate blood levels to 0.5 mM to 20 mM, eg 2 mM to 7.5 mM as. . .

SUMM It will be realised that treatment for neurodegenerative diseases such as **Alzheimer**'s will most effectively be given soon after identifying patient's with a predisposition to develop the disease. Thus treatment for **Alzheimers**' most effectively follows a positive test result for one or more conditions selected from the group (i) mutations in the. . . the presenilin gene on chromosome 14, (iii) presence of isoforms of apolipoprotein E. Other tests shown to be indicative of **Alzheimer**'s will of course be applicable.

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L7 ANSWER 4 OF 4 USPATFULL

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AN 2001:44413 USPATFULL

TI Therapeutic compositions

IN Veech, Richard L., Rockville, MD, United States

PA BTG International Limited, London, United Kingdom (non-U.S. corporation)

PI US 6207856 B1 20010327

AI US 2000-630007 20000731 (9)

RLI Division of Ser. No. US 1999-397100, filed on 16 Sep 1999 Continuation of Ser. No. WO 1997-US9805072, filed on 17 Mar 1997

PRAI US 1997-40858 19970317 (60)

DT Utility

FS Granted

EXNAM Primary Examiner: Reamer, James H.

LREP Nixon & Vanderhye
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN 2 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 1949
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
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